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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/791,618	03/02/2004	Sherman Fong	P1192-2C1	4005

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EXAMINER	
DEBERRY, REGINA M	
ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/791,618	FONG ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/06,10/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 17 October 2006 has been entered.

Information Disclosure Statement

The information disclosure statement(s)(IDS) filed 07 April 2006 and 17 October 2006 were received and comply with the provisions of 37 CFR §§1.97 and 1.98. They have been placed in the application file and the information referred to therein has been considered as to the merits.

Status of Application, Amendments and/or Claims

The amendment filed 17 October 2006 has been entered in full or part. Claims 11 and 15-18 were cancelled. Claims 12-14 are pending and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 101

Claims 12-14 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the isolated polypeptide. The basis for this rejection is set forth at pages 2-9 of the previous Office Action (27 January 2006).

The instant claims are drawn to methods of enhancing the infiltration of immune cells in a mammal, comprising administering to said mammal an effective amount of Bolekine polypeptide (SEQ ID NO:2) and a method of alleviating infection in a mammal comprising administering an effective amount of Bolekine polypeptide (SEQ ID NO:2).

Example 10 teaches the stimulatory activity of the Bolekine polypeptide in a mixed lymphocyte reaction (MLR). Example 11 demonstrates that the Bolekine polypeptide can induce inflammation at the site of injection in an animal (pages 87-88). The claimed invention is not supported by a specific or substantial utility because there is no information regarding the correlation of the results of the mixed lymphocyte reactions (results from Example 10) of the Bolekine polypeptide to any real life diseases. The specification fails to teach where an enhancement of an immune response is beneficial and therapeutically useful. Furthermore, the specification does not disclose how the induction of inflammation (results from Example 11) is beneficial and therapeutically useful. There is no information regarding which subsets of immune responses, immune cell types, etc. are targeted by compounds with activities in MLR. There is no correlation to the predisposition of a particular disease and the claimed

invention and/or how the results from Examples 10 and 11 correlate to a substantial utility. Further experimentation is required before this asserted utility is substantial.

The ability to stimulate or inhibit lymphocyte Bolekine proliferation in the MLR assay is an artificial *in vitro* system and does not provide for what specific conditions or for which specific diseases the claimed invention would predictably function. The assertion that the claimed invention could be useful for the treatment of conditions where the enhancement of the immune response would be beneficial is not specific since there are many such conditions, and it is not predictable of which conditions the claimed invention may function, if any. The specification fails to provide any data or evidence of the results of the assay, therefore, one of ordinary skill in the art cannot evaluate the conclusion. The specification states that "positive increases over control are considered positive", however, this does not indicate that statistical significance must occur for determination of a positive result in the assay. In conclusion, the results of the MLC (a.k.a. MLR) assay do not support a specific and substantial utility for the claimed invention because the assay is not predictive of immune response in general, and one of ordinary skill in the art would not expect a stimulatory effect in the MLC assay to correlate to a general stimulatory effect on the immune system, absent evidence to the contrary.

Thus, the proposed uses of the Bolekine polypeptides are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a either a credible, specific and substantial asserted utility or a well established utility.

Applicant discusses the Examiner's previous rejection. Applicant contends that the instant specification teaches where the enhancement of an immune response is beneficial and therapeutically useful. Applicant argues that it is well established that information which is well known in the art does not have to be described in detail in the specification. Applicant cites MPEP 601. Applicant argues that at the time the present application was filed, one of ordinary skill would have clearly been able to identify conditions where the enhancement of immune response is beneficial. Applicant cites submitted references (McElrath et al., McDyer et al., Zaki et al. and Tyring et al.). Applicant takes issue with the Examiner's statement that the claimed invention is not specific. Applicant argues that there are many conditions benefiting from the claimed invention. Applicant argues that the claims are not directed to Bolekine polypeptides or the treatment of conditions where the enhancement of the immune response in general would be beneficial. Applicant contends that claims 12 and 13 specify methods directed to the enhancement of the infiltration of immune cells in a

mammals and it is clear that any condition characterized by the suppression of immune response, such as immune related disorders would be expected to benefit from such infiltration.

Applicant's arguments have been fully considered but are not found to be persuasive. As was stated above, Example 10 teaches the stimulatory activity of the Bolekine polypeptide in a mixed lymphocyte reaction (MLR). Example 11 demonstrates that the Bolekine polypeptide can induce inflammation at the site of injection in an animal (pages 87-88). A specific utility is a utility that is specific to the subject matter claimed. The Examiner understands that there are conditions where the enhancement of an immune response is beneficial. The instant specification fails to teach those conditions specific to Bolekine polypeptides. The ability to stimulate or inhibit lymphocyte Bolekine proliferation in the MLR assay is an artificial *in vitro* system and does not provide for what specific conditions or for which specific diseases the claimed invention would predictably function. The assertion that the claimed invention could be useful for the treatment of conditions where the enhancement of the immune response would be beneficial is not specific since there are many such conditions, and it is not predictable of which conditions the claimed invention may function, if any.

Applicant takes issue with the Examiner's criticism of the MLR assay. Applicant argues that it is well established that the MLR assay is any art accepted assay for identifying immune suppressive molecules and that the assay is generally predictive of their in vivo effectiveness. Applicant submits U.S. Patent No. 5,817,306 and Dziarski to support their assertion.

Applicant's arguments have been fully considered but are not found to be persuasive. Dziarski teach the enhancement of MLR and cytotoxic antitumor responses by heparin. Dziarski teaches the increase DNA synthesis in responding lymphocytes, increased activity of cytotoxic cells, demonstrated that the activity was specific to heparin and that heparin enhanced cytotoxic cells were indeed CTL. Dziarski employed various assays to discern biological activity. The instant specification fails to do this. Regarding U.S. Patent No. 5,817,306, each Patent Application is examined on its own merits. What was deemed allowable in one Patent has no bearing on this application. Furthermore, the Examiner notes that the references cited by Applicants (U.S. Patent No. 5,817,306 and Dziarski) are drawn to proteins that were previously known or suspected to be involved in immune responses (e.g. heparin, IL-1 and IL-2). The Bolekine polypeptide is a totally new, uncharacterized polypeptide with no well-established utility.

Applicant discusses the previously submitted Fong Declaration. Applicant contends that two declarations by Dr. Fong were submitted and that the Examiner has given no reasons by the Fong declaration concerning the MLR assay has not been found convincing. Applicant discusses the Fong Declaration regarding the MLR assay.

Applicant's arguments have been fully considered but are not found to be persuasive. Both Fong declarations were considered as well as all of the other evidence of records. The Examiner stated, "in support of the MLR assay and the Vascular Permeability Assay, a declaration under 37 CFR 1.132 from Dr. Sherman Fong has been submitted". The Examiner discussed the problems with the MLR assay

(previous Office Action, page 4) and believed that is was clear from the body of the office action and the preponderance of the totality of evidence that the Fong Declaration regarding the MLR assay was not persuasive for withdrawing the rejection. The Examiner went into more depth with the Fong Declaration regarding the Vascular Permeability Assay. Nonetheless, the Examiner will discuss the Fong Declaration regarding the MLR assay.

Dr. Fong discusses the MLR assay and dendritic cells. Dr. Fong cites general background references (Current Protocols in Immunology and Steinmann) with which the Examiner takes no issue with. Dr. Fong states that immune stimulants find important clinical applications. Dr. Fong states that IL-12, a known immune stimulant, has been shown to stimulate T cell proliferation in the MLR assay and was first identified in just such an MLR assay. Dr. Fong cites Gubler et al. Dr. Fong discusses the immune stimulatory activity of IL-12 for treating cancer. This is not found persuasive. Gubler et al. also employed a Cr-release assay to discern cytotoxicity (figure 3, lower panel). This particular assay was also employed by Dziarski (reference submitted by Applicant). Furthermore, Gubler et al. state, in addition to the biologic activities described in this report, CLMF (IL-12) by itself has been shown to activate NK cells, to facilitate the generation of specific allogenic CTL responses and to stimulate the secretion of gamma interferon by resting peripheral blood lymphocytes. It can also synergize with low concentrations of recombinant IL-2 in the latter two assays and in causing the proliferation of resting peripheral blood lymphocytes. Even after the data, Gubler et al. concludes, "the availability of the recombinant CLMF will now make

possible a broader and more detailed characterization of its biology" (last page). Gubler, like Dziarski, employed other assays to characterize the protein. In contrast to these studies, there is no well characterized structure/function analysis in the specification for the Bolekine protein. Regarding the other references (Thurner et al. and Peterson et al.), the Examiner does not doubt that immune stimulants find important clinical applications. Such a role has not been suggested by the instant disclosure for the Bolekine polypeptide.

Applicant discusses the second Fong Declaration with respect to the Skin Vascular Permeability Assay. Applicant's arguments have been fully considered but are not found to be persuasive. The instant declaration has already been fully addressed on the record and is insufficient for overcoming the rejection for reasons of record. Furthermore, the Examiner did not mention undue experimentation in the 101 rejection. The Examiner stated, "the observation is merely a jumping-off point, that is, an invitation to experiment further to determine the properties of Bolekine". Lastly, the Examiner's statement, "the Declarant is not entirely correct with respect to the facts" was made because those teachings were not disclosed in the specification as originally filed.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

Claims 12-14 remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The basis for this rejection is set forth at page 10 of the previous Office Action (27 January 2006).

Applicant incorporates their response to the rejection under 35 USC 101 in response to the rejection under 35 USC 112, first paragraph. Applicants arguments have been fully considered but are not found to be persuasive for reasons of record and the reasons discussed above in the maintained rejection in 35 USC 101. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Conclusion

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A

shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action.

In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

RMD
1/6/07

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